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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/12, C07K 14/71, 16/28 C12N 15/62, G01N 33/68, A61K 38/17, A01K 67/027, C12N 5/10, A61K 39/00		A3	(11) International Publication Number: WO 97/33912 (43) International Publication Date: 18 September 1997 (18.09.97)
(21) International Application Number: PCT/US97/04363 (22) International Filing Date: 13 March 1997 (13.03.97) (30) Priority Data: 08/615,902 14 March 1996 (14.03.96) US 08/618,236 14 March 1996 (14.03.96) US (60) Parent Applications or Grants (63) Related by Continuation US 08/615,902 (CIP) Filed on 14 March 1996 (14.03.96) US 08/618,236 (CIP) Filed on 14 March 1996 (14.03.96) (71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KLEIN, Robert, D. [US/US]; 466 Baden Avenue #4, South San Francisco, CA 94080 (US). MOORE, Mark, W. [US/US]; 1301 Diamond Street, San Francisco, CA 94131 (US). ROSENTHAL, Amon [IL/US]; 1064 Glacier Avenue, Pacifica, CA 94044		(US). RYAN, Anne, M. [US/US]; 70 Broadway #9, Millbrae, CA 94030 (US). (74) Agents: TORCHIA, Timothy, E. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080-4990 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims</i> <i>and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 5 February 1998 (05.02.98)	
(54) Title: USES OF GDNF AND GDNF RECEPTOR			
(57) Abstract <p>GDNFRα, GDNFRα extracellular domain (ECD), GDNFRα variants, chimeric GDNFRα (e.g., GDNFRα immunoadhesin), and antibodies which bind thereto (including agonist and neutralizing antibodies) are disclosed. Various uses for these molecules are described, including methods to modulate cell activity and survival by response to GDNFRα-ligands, for example GDNF, by providing GDNFRα to the cell. Also provided are methods for using GDNFRα, GDNF, or agonists thereof, separately or in complex, to treat kidney diseases.</p>			

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INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/US 97/04363

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/71 C07K16/28 C12N15/62 G01N33/68
A61K38/17 A01K67/027 C12N5/10 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 06116 A (SYNTEX-SYNERGEN NEUROSCIENCE JOINT VENTURE) 1 April 1993 cited in the application see claims; examples 5-8 ---	1-31, 34-40
A	QIA YAN ET AL : "In vivo neurotrophic effects of GDNF on neonatal and adult facial motor neurons" NATURE, vol. 373, 26 January 1995, LONDON GB, pages 341-344, XP002036574 cited in the application see the whole document --- -/-	34-40

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

25 November 1997

Date of mailing of the international search report

15-12-1997

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Le Cornec, N

INTERNATIONAL SEARCH REPORT

Intern 1st Application No
PCT/US 97/04363

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. SCHUCHARDT ET AL: "Defects in the kidney and enteric nervous system of mice lacking the Tyrosine kinase Receptor Ret" NATURE, vol. 367, 27 January 1994, LONDON GB, pages 380-383, XP002036575 see the whole document ---	34-40
P,X	SHUQIAN JING ET AL: "GDNF-induced activation of the Ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF" CELL, vol. 85, 28 June 1996, NA US, pages 1113-1124, XP002036435 see the whole document ---	1-4,6,7, 11-13, 21, 23-31, 34-40
T	J.G. PICHEL ET AL: "GDNF is required for kidney development and enteric innervation" COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY 1996, vol. 61, 14 May 1997, pages 445-457, XP002047356 see the whole document ---	34,35, 38,39
A	ORTH S.R. ET AL: "Glial cell line -Derived Neurotrophic Factor (GDNF) in the kidney" JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 6, no. 3, September 1995, page 774 XP002047357 see abstract 559 ---	34,35,37
A	M. TRUPP ET AL: "Peripheral expression and biological activities of GDNF, a new neurotrophic factor for avian and mammalian peripheral neurons" THE JOURNAL OF CELL BIOLOGY., vol. 130, no. 1, July 1995, LER UNIVERSITY PRESS US, pages 137-148, XP002047358 see page 142, right-hand column - page 143, left-hand column see page 146, left-hand column ---	34,35,37
P,X	J.G. PICHEL ET AL: "Defects in enteric innervation and kidney development in mice lacking GDNF" NATURE., vol. 382, 4 July 1996, LONDON GB, pages 73-76, XP002047359 see the whole document ---	34,35, 38,39
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/04363

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>M. SAARMA ET AL: "Roles of GDNF in the development of nervous system and kidney" INTERNATIONAL JOURNAL OF DEVELOPMENT NEUROSCIENCE, vol. 14, no. suppl1, 1996, page 77 XP002047360 & 11TH BIENNIAL MEETING OF THE INTERNATIONAL SOCIETY FOR DEVELOPMENTAL NEUROSCIENCE, 30 July 1996 - 3 August 1996, TAMPERE, FINLAND, see abstract 110 -----</p>	<p>34,35, 38,39</p>

INTERNATIONAL SEARCH REPORT

I: national application No.

PCT/US 97/04363

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
See annex
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See annex

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 97/04363

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The application contains the following inventions:

YES- 1) claims 1-33; (36-37,40) partially :Rat GDNF Receptor alpha and its nucleic acid , a process for producing said protein by genetic engineering , a chimeric protein .Use of GDNFR-alpha in a method of treatment in combination with GDNF or GDNF agonist .Uses of GDNFR-alpha for identifying and purifying a molecule ,for modulating a physiological response of a cell to GDNF .A non-human transgenic animal transformed for expression GDNFR-alpha. A non-human knock-out animal having an altered GDNFR-alpha gene .An antibody against GDNFR-alpha and its uses.

NO- 2) claims 34-35; (36-37) partially : method of treating kidney disease comprising administering GDNF or GDNF agonist and optionnally further comprising administering GDNFR-alpha .

NO-3) claims 38-39;40 partially : method of treating an enteric nervous system-related disorder comprising administering GDNF or GDNF agonist and optionnally further comprising administering GDNFR-alpha.

REMARK : Although claims 11-13,20-21 (as far as in vivo methods are concerned) and claims 36 -37,40 are directed to a method of treatment of (diagnostic method practised on) the human/animal body (rule 39.1 (IV) PCT), the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/04363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9306116 A	01-04-93	AU 1900197 A	18-09-97
		AU 679167 B	26-06-97
		AU 2681192 A	27-04-93
		CA 2119463 A	01-04-93
		EP 0610254 A	17-08-94
		FI 941285 A	18-03-94
		HU 66137 A	28-09-94
		HU 9500478 A	30-10-95
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		MX 9205293 A	01-05-93
		NO 940922 A	19-05-94
		NZ 244392 A	28-03-95
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		ZA 9207159 A	02-08-93
